

What is claimed is:

1. A T cell receptor (TCR) comprising:
 - (a) a TCR α -chain variable (V_α) domain, and a TCR β -chain variable (V_β) domain having the CDR3 amino acid sequence set forth in SEQ ID NO.: 199 or 1;
 - (b) a TCR V_α domain having the CDR3 amino acid sequence set forth in SEQ ID NO.:196 or 12, and a TCR V_β domain; or
 - (c) a TCR V_α domain having the CDR3 amino acid sequence set forth in SEQ ID NO.:196 or 12 and a TCR V_β domain comprising the CDR3 amino acid sequence set forth in SEQ ID NO.:199 or 1,wherein the TCR binds to a VLDFAPPGA (SEQ ID NO.:59):human leukocyte antigen (HLA) complex.
2. The TCR of claim 1, which specifically binds to a VLDFAPPGA (SEQ ID NO.:59):HLA complex.
3. The TCR of claim 1 or 2, which specifically binds to a SEQ ID NO.:59 HLA complex with an IFN γ production pEC₅₀ of 8.5 or higher.
4. The TCR of any one of claims 1-3, wherein the TCR further specifically binds to the VLDFAPPGA (SEQ ID NO.:59):human leukocyte antigen (HLA) complex on a cell surface independent of CD8 or in the absence of CD8.
5. The TCR of any one of claims 1-4, wherein the HLA comprises HLA-A*201.
6. The TCR according to any one of claims 1-5, wherein:
 - (a) the V_α domain comprises an amino acid sequence that has at least about 90% sequence identity to the amino acid sequence set forth in SEQ ID NO.:34, and/or wherein the

V_α domain comprises no change in the amino acid sequence of CDR1 and/or CDR2 as compared to the CDR1 and/or CDR2, respectively, present in SEQ ID NO:34; and/or

(b) the V_β domain comprises an amino acid sequence that has about 90% sequence identity to the amino acid sequence set forth in SEQ ID NO.:23, and/or wherein the V_β domain comprises no change in the amino acid sequence of CDR1 and/or CDR2 as compared to the CDR1 and/or CDR2, respectively, present in SEQ ID NO.:23.

7. The TCR according to any one of claims 1-6, further comprising:

(i) the CDR1_α amino acid sequence set forth in SEQ ID NO.:194, or a variant thereof comprising one or two amino acid substitutions, wherein, optionally, the one or two amino acid substitutions comprise a conservative amino acid substitution; and/or

(ii) the CDR2_α amino acid sequence set forth in SEQ ID NO.:195, or a variant thereof comprising one or two amino acid substitutions, wherein, optionally, the one or two amino acid substitutions comprise a conservative amino acid substitution; and/or

(iii) the CDR1_β amino acid sequence set forth in SEQ ID NO.: 197, or a variant thereof comprising one or two amino acid substitutions, wherein, optionally, the one or two amino acid substitutions comprise a conservative amino acid substitution; and/or

(iv) the CDR2_β amino acid sequence set forth in SEQ ID NO.:198 or a variant thereof comprising one or two amino acid substitutions, wherein, optionally, the one or two amino acid substitutions comprise a conservative amino acid substitution.

8. The TCR according to any one of claims 1-7, comprising the CDR1_α, CDR2_α, CDR3_α, CDR1_β, CDR2_β, and CDR3_β amino acid sequences set forth in SEQ ID NOs.: 194, 195, 196 or 12, 197, 198, and 199 or 1, respectively

9. The TCR according to any one of claims 1-8, wherein the V_α domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:253 or 34, and/or

wherein the V_β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:242 or 23.

10. The TCR according to any one of claims 1-9, wherein:
- (i) the V_{α} domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:253; and
 - (ii) the V_{β} domain comprises or consists of the amino acid sequence set forth in SEQ ID NO:242.
11. The TCR according to any one of claims 1-10, wherein the TCR further comprises:
- (i) a TCR α -chain constant domain having at least about 90% sequence identity to the amino acid sequence of SEQ ID NO:47; and/or(ii) a TCR β -chain constant domain having at least about 90% sequence identity to the amino acid sequence of SEQ ID NO:45 or 46.
12. The TCR according to any one of claims 1-11, wherein the TCR comprises a TCR α -chain comprising a V_{α} domain and an α -chain constant domain, wherein:
- (a) the V_{α} domain has at least about 90% sequence identity to the amino acid sequence set forth in SEQ ID NO:34, and the α -chain constant domain has at least about 98% sequence identity to the amino acid sequence of SEQ ID NO:47;
 - (b) the V_{α} domain comprises the amino acid sequence set forth in SEQ ID NO: 253, and the α -chain constant domain comprises the amino acid sequence of SEQ ID NO:47; or
 - (c) the V_{α} domain consists of the amino acid sequence set forth in SEQ ID NO.: 253, and the α -chain constant domain consists the amino acid sequence of SEQ ID NO:47.
13. The TCR according to any one of claims 1-12, wherein the TCR comprises a TCR β -chain comprising a V_{β} domain and a β -chain constant domain, wherein the V_{β} domain has at least about 90% sequence identity to the amino acid sequence set forth in SEQ ID NO:23, and the β -chain constant domain comprises the amino acid sequence of SEQ ID NO:45 or has at least about 95% sequence identity to the amino acid sequence of SEQ ID NO:46

14. The TCR according to any one of claims 1-13, wherein the TCR comprises a TCR β -chain comprising a V_β domain and an β -chain constant domain, wherein:

(a) the V_β domain comprises the amino acid sequence set forth in SEQ ID NO:242, and the β -chain constant domain comprises the amino acid sequence of SEQ ID NO:45 or 46;

(b) the V_β domain consists of the amino acid sequence set forth in any one of SEQ ID NO: 242, and the β -chain constant domain consists of the amino acid sequence of SEQ ID

NO:45 or 46; or(c) the V_β domain comprises or consists of the amino acid sequence set forth in SEQ ID NO.:23, and the β -chain constant domain comprises or consists of the amino acid sequence of SEQ ID NO:46.

15. The TCR of any one of claims 1-14, comprising:

(i) a TCR α -chain comprising a V_α comprising SEQ NO.:253 and a C_α comprising SEQ ID NO.:47; and

(ii) a TCR β -chain comprising a V_β comprising SEQ NO.:242 and a C_β comprising SEQ ID NO.:46.

16. The TCR of any one of claims 1-15, wherein the TCR comprises a scTCR or a CAR.

17. An isolated polynucleotide encoding the TCR according to any one of claims 1-16.

18. The isolated polynucleotide of claim 17, wherein:

(i) the polynucleotide is codon optimized for a host cell of interest;

(ii) the polynucleotide has at least 75% identity to, comprises, or consists of the nucleotide sequence set forth in any one of SEQ ID NOs.:64, 75, 86, 97, 108, 109, 110, 111, 122, 133, and 144;

(iii) the polynucleotide has at least 95% identity to, comprises, or consists of the polynucleotide sequence set forth in SEQ ID NO.: 155; or

(iv) the polynucleotide encodes an amino acid sequence having at least 95% identity to, comprising, or consisting of the amino acid sequence set forth in SEQ ID NO.:48.

19. The polynucleotide according to claim 17 or 18, further comprising:

(i) a polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor α chain, wherein, optionally, the encoded polypeptide is or comprises a CD8 co-receptor α chain;

(ii) a polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor β chain, wherein, optionally, the encoded polypeptide is or comprises a CD8 co-receptor β chain; and/or

(iii) a polynucleotide of (i) and a polynucleotide of (ii), and optionally further comprising a polynucleotide encoding a self-cleaving peptide disposed between the polynucleotide of (i) and the polynucleotide of (ii).

20. The polynucleotide of claim 19, further comprising a polynucleotide that encodes a self-cleaving peptide and is disposed between:

(1) the polynucleotide encoding a binding protein and the polynucleotide encoding a polypeptide comprising an extracellular portion of a CD8 co-receptor α chain; and/or

(2) the polynucleotide encoding a binding protein and the polynucleotide encoding a polypeptide comprising an extracellular portion of a CD8 co-receptor β chain.

21. The polynucleotide of claim 19 or 20, comprising, operably linked in-frame:

(i) (pnCD8 α)-(pnSCP₁)-(pnCD8 β)-(pnSCP₂)-(pnTCR);

(ii) (pnCD8 β)-(pnSCP₁)-(pnCD8 α)-(pnSCP₂)-(pnTCR);

(iii) (pnTCR)-(pnSCP₁)-(pnCD8 α)-(pnSCP₂)-(pnCD8 β);

(iv) (pnTCR)-(pnSCP₁)-(pnCD8 β)-(pnSCP₂)-(pnCD8 α);

(v) (pnCD8 α)-(pnSCP₁)-(pnTCR)-(pnSCP₂)-(pnCD8 β); or

(vi) (pnCD8 β)-(pnSCP₁)-(pnTCR)-(pnSCP₂)-(pnCD8 α),

wherein pnCD8 α is the polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor α chain,

wherein pnCD8 β is the polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor α chain,

wherein pnTCR is the polynucleotide encoding a TCR,

and wherein pnSCP₁ and pnSCP₂ are each independently a polynucleotide encoding a self-cleaving peptide, wherein the polynucleotides and/or the encoded self-cleaving peptides are optionally the same or different.

22. The polynucleotide of any one of claims 19-21, wherein the encoded TCR comprises a TCR α chain and a TCR β chain, wherein the polynucleotide comprises a polynucleotide encoding a self-cleaving peptide disposed between the polynucleotide encoding a TCR α chain and the polynucleotide encoding a TCR β chain.

23. The polynucleotide of claim 22, comprising, operably linked in-frame:

- (i) (pnCD8 α)-(pnSCP₁)-(pnCD8 β)-(pnSCP₂)-(pnTCR β)-(pnSCP₃)-(pnTCR α);
- (ii) (pnCD8 β)-(pnSCP₁)-(pnCD8 α)-(pnSCP₂)-(pnTCR β)-(pnSCP₃)-(pnTCR α);
- (iii) (pnCD8 α)-(pnSCP₁)-(pnCD8 β)-(pnSCP₂)-(pnTCR α)-(pnSCP₃)-(pnTCR β);
- (iv) (pnCD8 β)-(pnSCP₁)-(pnCD8 α)-(pnSCP₂)-(pnTCR α)-(pnSCP₃)-(pnTCR β);
- (v) (pnTCR β)-(pnSCP₁)-(pnTCR α)-(pnSCP₂)-(pnCD8 α)-(pnSCP₃)-(pnCD8 β);
- (vi) (pnTCR β)-(pnSCP₁)-(pnTCR α)-(pnSCP₂)-(pnCD8 β)-(pnSCP₃)-(pnCD8 α);
- (vii) (pnTCR α)-(pnSCP₁)-(pnTCR β)-(pnSCP₂)-(pnCD8 α)-(pnSCP₃)-(pnCD8 β); or
- (viii) (pnTCR α)-(pnSCP₁)-(pnTCR β)-(pnSCP₂)-(pnCD8 β)-(pnSCP₃)-(pnCD8 α),

wherein pnCD8 α is the polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor α chain,

wherein pnCD8 β is the polynucleotide encoding a polypeptide that comprises an extracellular portion of a CD8 co-receptor α chain,

wherein pnTCR α is the polynucleotide encoding a TCR α chain,

wherein pnTCR β is the polynucleotide encoding a TCR β chain,

and wherein pnSCP₁, pnSCP₂, and pnSCP₃ are each independently a polynucleotide encoding a self-cleaving peptide, wherein the polynucleotides and/or the encoded self-cleaving peptides are optionally the same or different.

24. An expression vector, comprising the polynucleotide of any one of claims 17-23 operably linked to an expression control sequence.

25. The expression vector according to claim 24, wherein the vector is capable of delivering the polynucleotide to a host cell, wherein, optionally:

- (a) the host cell is a hematopoietic progenitor cell; or
- (b) the host cell is a human immune system cell, wherein, further optionally, the immune system cell is a CD4⁺ T cell, a CD8⁺ T cell, a CD4⁻ CD8⁻ double negative T cell, a $\gamma\delta$ T cell, a natural killer cell, a dendritic cell, or any combination thereof, wherein, still further optionally, the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, or any combination thereof.

26. The expression vector according to claim 24 or 25, wherein the vector is a viral vector, wherein, optionally, the viral vector is an adenoviral vector, a lentiviral vector, or a γ -retroviral vector.

27. A host cell, comprising the polynucleotide according to any one of claims 17-23 or the expression vector according to any one of claims 24-26, wherein the host cell expresses on its cell surface the TCR encoded by the polynucleotide.

28. The host cell according to claim 27, wherein the host cell is a hematopoietic progenitor cell or a human immune system cell.

29. The host cell according to claim 28, wherein:

- (i) the immune system cell is a CD4⁺ T cell, a CD8⁺ T cell, a CD4⁻ CD8⁻ double negative T cell, a $\gamma\delta$ T cell, a natural killer cell, a natural killer T cell, dendritic cell, or any combination thereof, wherein, optionally, the combination, if present, comprises a CD4⁺ T cell and a CD8⁺ T cell; or(ii) the immune system cell is a T cell, wherein, optionally, the T cell is a naïve T cell, a central memory T cell, an effector memory T cell, or any combination thereof,

wherein, further optionally, the TCR has higher surface expression on the T cell as compared to an endogenous TCR.

30. The host cell of any one of claims 27-29, wherein the host cell is capable of killing:

- (i) a tumor cell of breast cancer cell line MDA-MB-468;
- (ii) a tumor cell of pancreatic adenocarcinoma cell line PANC-1;
- (iii) a tumor cell of breast cancer cell line MDA-MB-231;
- (iv) a tumor cell of myelogenous leukemia cell line K562 expressing an HLA-A2, wherein, optionally, the HLA-A2 comprises HLA-A*201;
- (v) a tumor cell of colon carcinoma cell line RKO expressing an HLA-A2, wherein, optionally, the HLA-A2 comprises HLA-A*201; or
- (vi) any combination of tumor cells of (i)-(v),

when the host cell and the tumor cell are both present in a sample, wherein, optionally, the host cell is capable of killing the tumor cell when the host cell and the tumor cell are present in the sample at a ratio of 32:1 host cell:tumor cell, 16:1, 8:1, 4:1, 2:1, or 1.5:1.

31. A composition, comprising the host cell of any one of claims 27-30 and a pharmaceutically acceptable carrier, diluent, or excipient, wherein, optionally, composition comprises a host CD4+ T cell and a host CD8+ T cell.

32. The host cell of any one of claims 27-30 or the composition of claim 31 for use in a method of treating a hyperproliferative or proliferative disorder in a subject, wherein the method comprises administering the host cell or composition to the subject.

33. The host cell or composition for use according to claim 32, wherein the hyperproliferative or proliferative disorder is a hematological malignancy or a solid cancer, wherein, optionally, the hematological malignancy is selected from acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma

(NHL), or multiple myeloma (MM), and/or the solid cancer is selected from breast cancer, ovarian cancer, lung cancer, biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma multiforme, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, mesothelioma, malignant melanoma, osteosarcoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, or uterine cancer.

34. The host cell or composition for use according to claim 32 or 33, wherein:
- (a) the subject is human; and/or
 - (b) the host cell is modified *ex vivo*, wherein, optionally, the host cell is an allogeneic cell, a syngeneic cell, or an autologous cell to the subject; and/or
 - (c) the host cell is formulated for parenteral administration, wherein, optionally, the host cell is formulated for administration to the subject at a dose of about 10^7 cells/m² to about 10^{11} cells/m²; and/or
 - (d) the host cell or composition is formulated for administering a plurality of doses of the host cell to the subject, wherein, optionally, the plurality of doses are formulated for administration at intervals between administrations of about two to about four weeks; and/or
 - (e) the subject is further receiving immunosuppressive therapy, wherein, optionally, the immunosuppressive therapy is selected from calcineurin inhibitors, corticosteroids, microtubule inhibitors, low dose of a mycophenolic acid prodrug, or any combination thereof; and/or
 - (f) the subject has received a non-myeloablative or a myeloablative hematopoietic cell transplant; wherein, optionally, the subject is administered the host cell at least three months after the non-myeloablative hematopoietic cell transplant; wherein, further optionally, the subject is administered the host cell at least two months after the myeloablative hematopoietic cell transplant; and/or

(g) the subject has received or is receiving an immune checkpoint inhibitor and/or an agonist of a stimulatory immune checkpoint agent.

35. A unit dose form comprising the host cell according to any one of claims 27-30 or the composition of claim 31, wherein the host cell is at a dose of about 10^7 cells/m² to about 10^{11} cells/m².

36. The TCR of any one of claims 1-16, the polynucleotide of any one of claims 17-23, the expression vector of any one of claims 24-26, the host cell of any one of claims 27-30, or the composition of claim 31, or any combination thereof, for use in therapy.

37. Use of the TCR of any one of claims 1-16, the polynucleotide of any one of claims 17-23, the expression vector of any one of claims 24-26, the host cell of any one of claims 27-30, or the composition of claim 31, or any combination thereof, in the manufacture of a medicament for treating of a proliferative or hyperproliferative disorder associated with Wilms tumor protein 1 (WT1) expression or overexpression.

38. The use of claim 37, wherein the proliferative or hyperproliferative disorder associated with Wilms tumor protein 1 (WT1) expression or overexpression is a hematological malignancy or a solid cancer.

39. The use of claim 38, wherein:

(i) the hematological malignancy is selected from acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), chronic eosinophilic leukemia (CEL), myelodysplastic syndrome (MDS), non-Hodgkin's lymphoma (NHL), or multiple myeloma (MM); and/or

(ii) the solid cancer is selected from breast cancer, ovarian cancer, lung cancer, biliary cancer, bladder cancer, bone and soft tissue carcinoma, brain tumor, cervical cancer, colon cancer, colorectal adenocarcinoma, colorectal cancer, desmoid tumor, embryonal cancer, endometrial cancer, esophageal cancer, gastric cancer, gastric adenocarcinoma, glioblastoma

multiforme, gynecological tumor, head and neck squamous cell carcinoma, hepatic cancer, mesothelioma, malignant melanoma, osteosarcoma, pancreatic cancer, pancreatic ductal adenocarcinoma, primary astrocytic tumor, primary thyroid cancer, prostate cancer, renal cancer, renal cell carcinoma, rhabdomyosarcoma, skin cancer, soft tissue sarcoma, testicular germ-cell tumor, urothelial cancer, uterine sarcoma, or uterine cancer.